

## Lynne Howell, PhD

- Research Institute, Molecular Structure & Function, Head and Senior Scientist
- University of Toronto, Biochemistry, Professor
- Canada Research Chair, Structural Biology

We are interested in the chronic bacterial infections that occur the lungs of Cystic fibrosis (CF) patients, specifically the bacterial biofilms or the polymers that are produced to form the bacterial biofilms. We are studying how three different sugar polymers are produced with the long-term goal of identifying novel strategies to prevent their enhanced biofilm formation.

The reason that we are interested in bacterial biofilms as a whole is that once the biofilm is created, the bacteria that are embedded within the biofilm are difficult to eradicate and get rid of and they can avoid the host immune response. The inability of the host immune response to clear the bacteria ultimately leads to damage in the surrounding lung tissues. Over a longer term, this causes irreversible lung damage that ultimately requires the patient to have lung transplant.

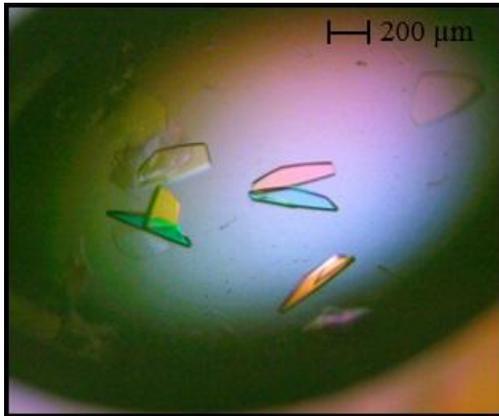
If we can develop novel therapeutics that can prevent formation of these sugar polymers, we should be able to control the bacterial infections and hopefully lead to improved lung function over a longer period of time.

The second aspect of our lab work is a collaborative project with Dr. Lori Burrows of McMaster University, which is looking at the assembly and disassembly of a bacterial organelle in *Pseudomonas* called Type IV pilus. *Pseudomonas* is the most prevalent bacteria in the lungs of CF patients, and the Type IV pilus is needed to be able to attach to surfaces, so it is the first part of the process in biofilm formation.

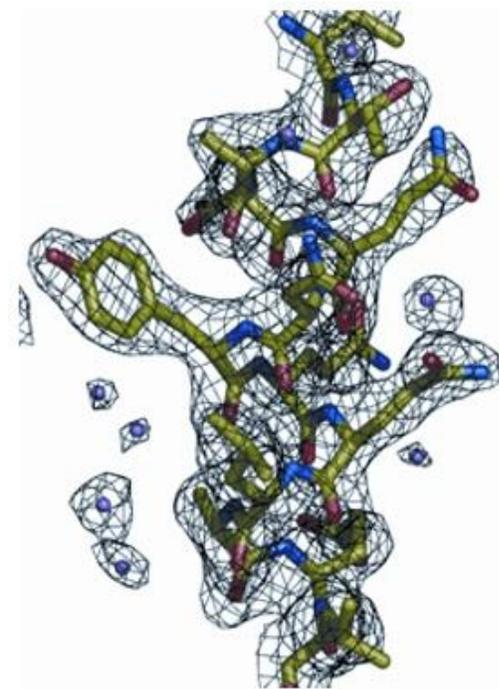
I took an undergraduate degree in biophysics, multidisciplinary training in a large number of different areas including structural biology. Rare for Britain, it was a four year degree that involved a large amount of research in the final year. I suppose my curiosity in how things function at a molecular level triggered my interest and started me off on my career in science and research, and I have been going in that direction ever since.

My work in cystic fibrosis was motivated by the expertise and strength of the research at SickKids and its surrounding area, as well my interest in the production of carbohydrate polymers. When our lab was looking for a new project, I had a conversation with Lori Burrows, and that was how we started on first Type IV pilus project, and subsequently the carbohydrate synthesis project.





**Fig. 1: Protein crystals:** *Structure determination of the protein of interest starts with the production of large quantities of protein that are subsequently crystallized using vapour diffusion techniques.*



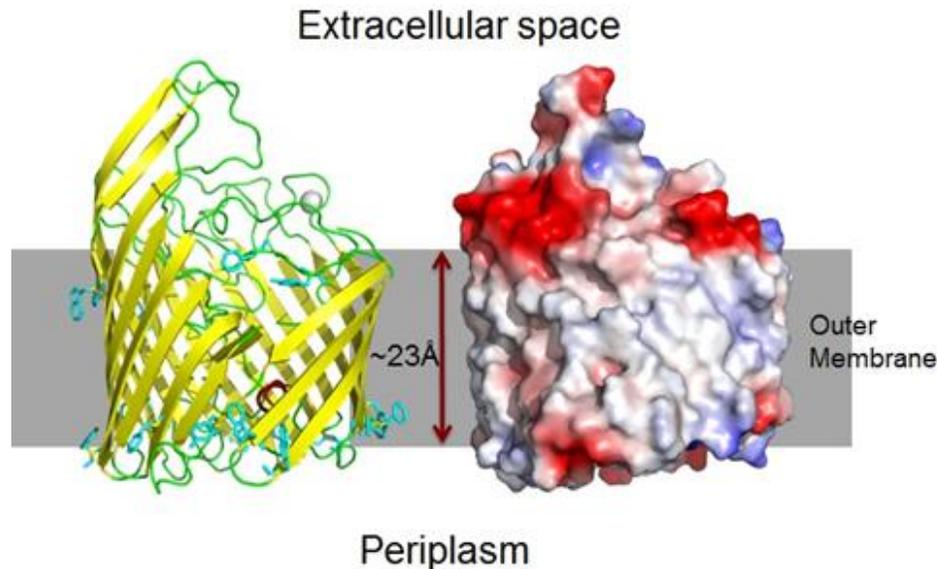
**Fig. 2: Electron density and modeled protein structure:** *Crystals are irradiated with X-rays and once phases for each amplitude or data point measured are obtained, we can calculate an electron density map. This map represents the distribution of electrons in the protein and can be used to build a model of the protein of interest.*

[Click here for a complete list of Dr. Lynne Howell's publications at NCBI PubMed.](#)

**Trainees:**

**Perrin Baker (post-doctoral fellow), Noor Alnabelseya (graduate student), Greg Whitfield (graduate student) and Lindsey Marmont (graduate student)** are looking at a polymer called the Pel polysaccharide. In particular, Baker and Alnabelseya have determined through collaboration with Matthew Parsek of the University of Washington that the deacetylase activity of PelA is required for biofilm formation. They are looking at the structure and function of this protein and are developing a high throughput assay to identify inhibitors of the activity. Whitfield and Marmont are working on other proteins involved in the production of the Pel polysaccharide.

**Laura Riley (post-doctoral fellow), Francis Wolfram (post-doctoral fellow), and Tyler Ricer (graduate student), and Perrin Baker** have been involved in looking at various proteins involved in alginate production, which is a major polysaccharide implicated in biofilm formation in the lungs of patients with CF. Each individual is looking at a particular protein involved various stages in this process with the idea of gaining an understanding of the structure and function of the protein, so that we can subsequently use this data to look at novel ways of preventing alginate production. Specifically, Riley is looking at a protein called AlgX, Ricer is working on AlgJ, Wolfram is working on AlgG and AlgL, and Baker is helping to develop assays to characterize the proteins.



**Fig. 3: Structure of AlgE involved in export of alginate:** *Cartoon representation of AlgE (left panel) and the corresponding surface representation with red depicting areas of negative charge, white neutral and blue positive charge (right panel).*

**Jason Koo (post-doctoral fellow)** and Matthew McCallum (graduate student) are looking at trying to understand various aspects of the assembly mechanism of the Type IV pilus organelle. In particular Koo is looking at the mechanism of the export of the Type IV pilus through the outer membrane using cryo-electron microscopy. The idea is to try to understand how the Type IV pilus is assembled and to find novel ways to prevent its assembly.

[SickKids Hospital > Lynne Howell Profile](#)

[SickKids Hospital > Research > Howell Lab](#)

[University of Toronto > Department of Biochemistry > Lynne Howell Profile](#)